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10/618,088	07/14/2003	Elizabeth Jaffee	001107.00363	4098

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,088	JAFFEE ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-38,111 and 113-121* is/are pending in the application.

4a) Of the above claim(s) *25,116 and 120* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,26-38, 111, 113-115, 117-119 and 121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/18/08 has been entered.

2. Claims 22- 38, 111, and 113-121 are all the pending claims for this application.

3. New claims 116-121 were added in the Response of 1/18/08.

4. Claim 25 is withdrawn from examination. New Claim 116 is withdrawn as being drawn to a non-elected species of cancer for mesothelioma. New Claim 120 is withdrawn as depending from withdrawn Claim 25. The non-elected species of cancer for ovarian cancer, mesothelioma and squamous cell carcinoma in Claim 23 are withdrawn.

5. Claims 22-24, 26-38, 111, 113-115, 117-119 and 121 are all the pending claims under examination with species to pancreatic cancer.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The rejection of Claims 22-24, 26-38, 111, 113-115 (and new Claims 117-119 and 121) under 35 U.S.C. 112, first paragraph, in lacking enablement is maintained for reasons of record as set forth in the Office Actions of 10/30/06, 7/19/07 and hereinafter.

The claims are drawn to inducing a T cell response against a mesothelin-overexpressing pancreatic cancer in any subject including a human where the T cell response is required to be sufficiently induced by an expression product from a polynucleotide (*DNA gene therapy*) encoding one or more MHC class I binding epitope(s) of mesothelin. The claims require that the T cell response should induce tumor regression or keep the patient tumor-free after removal of the tumor.

The summary of evidence provided in Exhibit A is acknowledged and the additional evidence provided in Exhibits B-N is discussed below. When the evidence of record is viewed in its *totality* and *as a whole*, Applicants have yet to provide a single piece of corroborating evidence demonstrating that the actual claimed method steps of the invention encompassing DNA gene therapy can be practiced both reproducibly and reliably in any animal model much less in a human pancreatic cancer subject by one of ordinary skill in the art.

A) <u>WF-3 animal model/ WF-3 tumor cells in vitro</u>

In the Office Action of 7/19/07, the Examiner stated:

"Applicants were the first to describe the WF-3 animal model in Examples 6-11 of the specification. WF-3 as discussed during the interview of March 14, 2007 is a mesothelin-expressing cell line and *not a pancreatic cancer cell line*. Applicants stated on the record, that there is no known model for a human mesothelin-expressing pancreatic cancer and that the cell line was modified to create a high level, mesothelin-expressing model. WF-3 cells do not appear to invade the pancreas but grow in the peritoneum as ascites of adoptive C57BL/6 mice.

Significantly, Applicants allege on p. 10, lines 4-5 of the Response of 4/30/07 "Induction of mesothelin-specific cytotoxic T lymphocytes is not specifically shown in this model." Instead, "The effect is shown by increased survival" (p. 10, line 3). Then in the Jaffee Declaration at [15-19], specifically at [19], Jaffee alleges "the DNA vaccine was shown to be capable of inducing mesothelin-specific T-cell mediated specific lysis of

WF-3 cells (Example 11 and Figure11)"..."a mesothelin-encoding DNA vaccine composition can generate mesothelin-specific, antitumor T-cell immune responses in a mammal..." Based on the foregoing, Applicants appear to be drawing distinctly opposite or at least contrasting conclusions about the CTL-inducing effects of the DNA therapy in the WF-3 model. Applicants own interpretation of the results for DNA therapy in the WF-3 animal model is inconclusive.

The DNA therapy appears to provide for increased survival of mice in the WF-3 model although it is not clear if this is under disease-free conditions and what if any other natural mesothelin-expressing cancer the DNA therapy could be used to treat. It is not demonstrated that the DNA therapy induces tumor regression. One skilled in the art could not reasonably extrapolate any of these findings to treating mesothelin-expressing pancreatic tumors in a human patient with any kind of DNA-mesothlin therapy."

Applicants' allegations on pp. 7-8 of the Response of 1/18/08 and the Cheng reference (Exhibit B) have been considered.

Applicants have established that the clonotypic, mesothelin-expressing, murine-derived WF-3 cell line can be used *in vivo* as a peritoneal-based, syngeneic mouse model for studying ovarian cancer, mesothelioma and pancreatic cancer, and *in vitro* for demonstrating specific T-cell lysis of the cell line (Exhibit B).

However, none of the data from the experiments in the specification or the Declaration evidence of Dr. Jaffe from 4/30/07 show *DNA*-based therapy. All of the experimentation and evidence of record relies on administering Listeria-expressing mesothelin in the WF-3 mouse model or Listeria-expressing mesothelin in humans with lung nodules.

Where have applicants shown administration of a <u>polynucleotide</u> encoding the mesothelin epitopes (SEQ ID NOS: 1-6) to any pancreatic cancer patient subject (e.g., a WF-3-bearing mouse model, a human pancreatic cancer animal model or a human pancreatic cancer patient in vivo)?

B) Listeria animal model

In the Office Action of 7/19/07, the Examiner stated:

"Applicants' Response of 4/30/07 on p. 10 refers to the discussion in the Jaffee Declaration at [20-27] regarding examples of independent studies using Listeria-based mesothelin-encoding vaccines in mouse models.

The Jaffee Declaration summarizes Examples 31B-31D of US2005/0249748 alleges that because the inventive peptides (SEQ ID NO:2-5) are inherent to the mesothelin of US2005/0249748, one of skill in the art would be enabled to practice the inventive method in humans suffering from or having had a tumor removed, especially a pancreatic tumor, using a mesothelin-expressing Listeria monocytogenes bacterium as a delivery vehicle.

The Examiner respectfully disagrees that US2005/0249748 is any more enabling for the inventive method using a recombinant mesothelin-expressing Listeria monocytogenes bacterium because no where in Examples 31B-31D is it shown that a) a xenogenic human pancreatic carcinoma in a mouse model has been tested, b) that the bacterium would induce an epitope specific CTL response in a pancreatic cancer model, c) the composition comprising both a polynucleotide encoding mesothelin and recombinant mesothelin-expressing Listeria monocytogenes would be effective, d) the composition induces tumor regression, and c) the composition keeps the mouse tumor free after removal of the tumor.

At [25-26], the Jaffee Declaration summarizes the studies presented in a poster from a SPORE Meeting (Exhibit 6) which is entitled "CRS-207: Live-attenuated Listeria monocytogenes encoding mesothelin for immunotherapy of patients with pancreatic and ovarian cancers."

The poster abstract does not show any studies on human pancreatic cancer being treatable with a mesothelin-expressing Listeria monocytogenes bacterium. The only studies described are those in a lung tumor nodule model using the mesothelin-expressing Listeria-based delivery. Thus, the poster abstract is not on point with the instant method claims for a pancreatic cancer.

Further, the instant claims are not drawn to an attenuated or modified bacterium that is otherwise rendered exo- or endotoxin-free, thus it is not understood how one of skill in the art could even practice the method using a composition comprising just any wild-type bacterium much less a Listeria without first producing a detrimental effect such as septic shock in the patient."

Applicants' allegations on pp. 8-11 of the Response of 1/18/08 have been carefully considered along with the references under Exhibits C and K-N.

i) Applicants have established the relevance of treating a lung tumor nodule in a human patient with mesothelin- expressing Listeria.

ii) Applicants have established that human xenograft models cannot be established for evaluation of the claimed therapy. According to Applicants, one of skill in the art could not examine a human xenografted pancreatic cancer in an immune competent mouse due to histo-incompatability, nor could they study induction of a CTL

specific response to a human xenograft pancreatic cancer in an immune incompetent (i.e., nude) mouse.

iii) Applicants have established that the recombinant Listeria described in US 2005/0249748 comprises a polynucleotide encoding a mesothelin-derived polypeptide and which expresses the full length protein. Applicants have shown that an attenuated recombinant Listeria encoding and secreting mesothelin has been submitted in December 2007 for Phase I clinical trial to treat human mesothelioma, adenocarcinoma of the pancreas, NSCLC and ovarian cancer (Exhibit C). Applicants have established the use of attenuated, engineered bacteria as potential vaccine vectors (Exhibits K-N).

However, Applicants have not shown that a naked DNA or naked expression vector or viral vector comprising polynucleotide expressing the full length mesothlin or peptide epitopes could be administered under the same conditions and produce the same results.

Where have applicants shown administration of a <u>polynucleotide</u> encoding the mesothelin epitopes (SEQ ID NOS: 1-6) to any pancreatic cancer patient subject (e.g., a WF-3-bearing mouse model, a human pancreatic cancer animal model or a human pancreatic cancer patient in vivo)?

C) <u>Phase I Clinical Trial/ Phase II Clinical Trials</u>

In the Office Action of 7/19/07, the Examiner stated:

"On pp. 10-11 of the Response of 4/30/07 and in the Jaffee Declaration at [6-11], Applicants discuss the results of a clinical trial with 14 human patients using a whole cell tumor vaccine comprising two GM-CSF- and mesothelin-expressing pancreatic cell lines and administered after the adenocarcinoma of the pancreas had been surgically resected from the patients (Thomas publication, Exhibit 2). The tumor vaccine produced mesothelin-specific CTLs in three of the patients against peptide of SEQ ID NO: 1-6 when PBLs were tested in

vitro. Applicants correlate these observations with long term disease-free survival and post-vaccination in vivo delayed type hypersensitivity (better clinical course) for the three patients.

Notably, the whole tumor vaccine does not in any way resemble the inventive reagent(s) of the instant claims. Thus Applicants have not demonstrated that any polynucleotide (in any form much less a recombinant Listeria monocytogenes) encoding mesothelin much less the inventive peptides would produce any such effects, i.e., induction of mesothelin-specific T cells through MHC class I binding, longterm disease-free survival and in vivo DTH responses to autologous tumor cells, in a human patient that meets all of the instant claims limitations.

Further it is noted that all of the patients had undergone surgery to render them essentially tumor-free (having minimal residual disease [7, line 3] of the Jaffee Declaration) and none of the evidence of record demonstrates efficacy for the inventive method in a human patient with a full, non-resected pancreatic tumor."

"On p. 11, ¶1 of the Response of 4/30/07 and in the Jaffee Declaration at [12-14], Applicants discuss the results of two Phase II clinical trials using the mesothelin-expressing whole tumor cell approach. Applicants describe induction of mesothelin-specific T cells in about 1/3 of the patients and correlate the prolonged, progression-free survival with the tumor cell approach. While these studies demonstrate that mesothelin is effective as an immune target for pancreatic carcinoma in humans, none of the trials appear to use a method, which even reads on the instant scope of the claims and would allow one of skill in the art to practice the method. None of the clinical trials methods resemble the instant polynucleotide reagents for performing the method MHC Class binding and epitope-specific CTL induction.

Despite Applicants assertions that the body of evidence supports a DNA (polynucleotide)-mesothelin based approach to pancreatic cancer therapy vis-à-vis CTL specific killing of tumor target, Applicants have not shown that any such approach has been or can be practiced in a human patient. For all of these reasons, the rejection of the claimed invention is maintained."

Applicants' allegations on pp. 11-12 of the Response of 1/18/08 have been considered.

Applicants have alleged by incorporation of the Hassan reference (Exhibit D), the art recognition of their whole tumor cell approach to vaccinating pancreatic cancer patients with GM-CSF transduced pancreatic cancer cell and for "the potential utility of mesothelin in peptide and/or vector-mediated immunotherapy."

The examiner respectfully submits that the instant claimed method invention specifically excludes a composition comprising whole tumor cells. Claim 22 in its entirety recites:

22. A method of inducing a T-cell response to a tumor which over expresses mesothelin relative to normal tissue from which it is derived, said method comprising: administering to a patient who has said tumor or who has had said tumor removed, a composition comprising a polynucleotide encoding a

polypeptide comprising an MHC Class I binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class I which is expressed by the patient, whereby a T-cell response to mesothelin is induced, *wherein the composition does not comprise whole tumor cells*. [Examiner's italics]

Where have applicants shown administration of a polynucleotide encoding the mesothelin epitopes (SEQ ID NOS: 1-6) to any pancreatic cancer patient subject (e.g., a WF-3-bearing mouse model, a human pancreatic cancer animal model or a human pancreatic cancer patient in vivo)?

D) Exhibits E-J – additional studies using mesothelin -based approaches for cancer therapy

Applicants have provided copies of the following references which they allege as further enabling the instant claimed method for treating pancreatic cancer:

Hung (Exhibit E) shows that a murine CTL response against a human mesothlin epitope (aa 540-549) using a DNA vaccine (pcDNA3-Hmeso540-β2m-A2) generated in HLA-A2 transgenic mice, and cytotoxic killing of a syngeneic, engineered mesothelin-expressing murine tumor cell line (TC-1/A2/Hmeso cell line; described on p. 129, Col. 1, ¶1-2). Hung teaches "Our study in the preclinical transgenic mouse model will likely serve as a solid foundation for future clinical translation of DNA vaccines for immunotherapy of gynecological cancers" (p. 134, Col. 2, last ¶). The tumor cell line of Hung was not a murine or human pancreatic cancer cell line and Hung does not contemplate treating pancreatic tumors.

Hung (Exhibit F) created a murine mesothelin-expressing tumor cell line (MOSEC/luc) to study ovarian cancer in mice. Murine mesothelin specific CD8+ T cells were generated against a DNA vaccine (pcDNA-Meso) in conjunction with the anti-apoptotic BAK and BAX siRNA and could be adoptively transferred into MOSEC/luc mice to control the tumors in vivo. The tumor cell line of Hung was not a murine or human pancreatic cancer cell line and Hung does not contemplate treating pancreatic tumors.

Chang (Exhibit G) created a murine ovarian cancer cell line expressing human mesothelin and that the tumor in mice could be controlled by treatment with Hmeso DNA vaccine, pcDNA2-Hmeso and that the effect was mediated by both CD4+ and CD8+ T cells. Chang explains that the *antibody response* generated in the mice against the DNA vaccine has led to “one early phase of clinical trials using humanized monoclonal antibodies against Hmeso in patients with mesothelin-expressing pancreatic cancer (Dr. Jaffe personal communication)" (p. 1195; Col. 1, ¶1). Notably, the article does not reference using the DNA vaccine *per se* in treating pancreatic cancer.

Dubesnky (Exhibit H) describes a live attenuated, Listeria based vaccine, Lm CRS-207 encoding human mesothelin, which in preclinical studies elicits CD4+/CD8+ T cells in mice and monkeys and will undergo clinical evaluation in subjects with pancreatic and ovarian cancer. Notably, the article does not reference using a DNA vaccine *per se* in treating pancreatic cancer.

Li (Exhibit I) uses a chimeric virus-like particle (VLP)-HMSLN encoding human mesothelin in C57BL/6J mice to treat pre-existing pancreatic tumor. Li explains that

MSLN expressing cell lines promote tumor progression in subcutaneous and orthotopic pancreatic cancer xenograft mouse models, and silencing MSLN expression (by what means?) ablated tumor growth. Li explains that the chimeric vector was tested in C57BL/J6 mice orhtotopically implanted with pancreatic tumors and tumors regressed compared to blank vector controls. Here it is not the least bit clear whether synegenic or human pancreatic tumor cells were used in the C57BL/J6 studies for the vector vaccine. Li distinguishes nude mice from the C57BL/J6 mice, but the actual cell lines used under either condition are not adequately explained.

Yokokawa (Exhibit J) describes a mesothelin CTL epitope and the ability of T cell lines generated from a pancreatic cancer patient to lyse mesothelin-expressing cancer cell lines in vitro (both pancreatic and ovarian cell lines). Notably, the article does not reference using a DNA vaccine *per se* in treating pancreatic cancer.

Examiner's Additional Comments

State of Art for In Vitro/ In Vivo Translation of Therapeutics

In addition to the references of record describing the complexity and unpredictability of pancreatic cancer treatment much less the selection and use of immunogenic peptide-based approaches (Yokokawa (2005); Stein WO 00/20027 (2000)), the Examiner draws Applicants attention to the critical examination of translational studies considered by Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse

allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11})

during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar.

Thus when viewed in light of the totality of the evidence, one skilled in the art could reasonably conclude that experimental data obtained in syngeneic or even xenograft mouse models would not necessarily correlate with results expected in human mesothelin pancreatic-expressing tumors.

State of Art for DNA Therapy/ Peptide Therapy

The claims are drawn to inducing a T cell response against a mesothelin-expressing pancreatic cancer in any subject including a human where the T cell response is required to be sufficiently induced by an expression product from a polynucleotide (*DNA gene therapy*) encoding one or more MHC class I binding peptide epitope(s) of mesothelin. Thus the claimed method combines two therapies with currently unpredictable successes; gene therapy and peptide therapy much less for their use in treating pancreatic cancer (see Examiner's cited references of record Shirle (2001); Anderson (2000); Feltkamp (1994); Beier (2004); Ezell (1995); Li (2004); Hassan (2004); Haupt (2002)).

Clinical trials of vaccination of cancer patients with MHC class-I restricted peptides derived from tumor antigens are presently ongoing worldwide. Although the results of some of these trials have shown evidence of immunogenicity of the selected peptides and formulations together with episodic clinical responses, their overall outcomes have failed to meet investigators expectations. Among others, one of the evocated explanations for the relatively poor outcome of tumor vaccines composed of

MHC class-I restricted peptides alone is the lack of simultaneous stimulation of CD4+ T cells that may be required for generating and sustaining vigorous antitumor immunity (Ayyoub et al. J. Immunol. 172:7206-7211 (2004)).

In 2007, Bijker et al. (Expert Rev. Vaccines 6(4):591-603 (2007)) expanded upon the idea that multiple peptide epitopes from tumor associated antigens for inducing both CD4+ and CD8+ T cell response would be more effective in obtaining a sustainable anti-tumor response (p. 592, Col. 2- p. 593, Col. 2). Table I of Bijker outlines several properties for optimized peptide vaccines: a) multiple epitopes for inducing CD4+/CD8+ T cell repertiore, b) broad applicability for HLA type, c) targeting to APCs, d) sustained duration of presentation, e) inclusion of CD4+ T cell help, f) inclusion of strong APC-activating signals, and g) APC presentation and APC-activating signals should be matched in time and proximity.

Glick (Gen. Engineer. News 28(7) pp. 6 and 9 (4/1/08)) recently overviewed the state of art for gene therapy and states: “It was not until the 1960’s that the first reports appeared indicating that mammalian cells could be genetically altered by means of isolated DNA. Years later, in 1990, the first successful example of gene therapy was demonstrated, albeit for a vary rare, life threatening disorder, severe combined immunodeficiency in a child lacking the normal gene for adenosine deaminase. A fair number of gene therapy clinical trials have been initiated since then and many are ongoing. If perfected, gene therapy might be of enormous practical value, saving countless lives and resulting in huge market opportunities. Yet thus far, over 60 years following the discovery that isolated DNA could genetically transform cells, only a

handful of companies have marketed gene therapy for a couple of conditions, and the number of patients treated, mostly outside of the U.S., is relatively small."

Conclusion

Applicants are urging the Office to consider the claims fully enabled for the breadth of scope based on the volume of exhibits "*taken as a whole*" as filed in the course of the prosecution proceeding. The instant claimed method combines two therapies with currently unpredictable successes; gene therapy and peptide therapy much less for their use in treating pancreatic cancer.

Where have applicants shown administration of a polynucleotide encoding the mesothelin epitopes (SEQ ID NOS: 1-6) to any pancreatic cancer patient subject (e.g., WF-3 mouse model, a human pancreatic cancer animal model or a human pancreatic cancer patient in vivo)?

Conclusion

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Partial Signatory Authority